

IN THE CLAIMS:

Please amend claims 1, 5-8, 21, 23, 46, 279, 307, 341, 345, 347 cancel claims 9-19, 43, 44, 47-74, 139-144, 306, 308, 315, 316, 332-340, 342, 344 and 346 without prejudice or disclaimer, and add claims 348-356. This listing of claims replaces all prior listings of claims.

LISTING OF CLAIMS:

1. (Currently amended) An isolated interferon (IFN) alpha cytokine, comprising ~~one or more~~ an amino acid replacement in its sequence of amino acids, whereby the interferon alpha cytokine exhibits increased resistance to proteolysis compared to the unmodified interferon alpha cytokine that does not comprise the amino acid replacement; ~~one or more amino acid replacements~~, wherein an amino acid replacement is E41Q or the corresponding position, based upon alignment, in the interferon-alpha cytokine.

2-4. (Cancelled)

5. (Currently Amended) The interferon alpha cytokine of claim 1, wherein the unmodified interferon alpha cytokine is selected from among an interferon α -2b (IFN α -2b), an interferon α -2a (IFN α -2a), an interferon α -2c (IFN α -2c), and ~~an~~ consensus interferon ~~having the sequence set forth in SEQ ID NO: 232.~~

6. (Currently amended) An interferon alpha cytokine of claim 1, wherein:
the modification is E41Q and is selected from among IFN α -2b, IFN α -2a, IFN α -2c,
consensus interferon, IFN α -c, IFN α -d, IFN α -5, IFN α -6, IFN α -4, IFN α -4b, IFN α -I, IFN α -J,
IFN α -H, IFN α -F and IFN α -8;

the sequence of a human wild-type interferon alpha for each of IFN α -2b, IFN α -2a,
IFN α -2c, consensus interferon, IFN α -c, IFN α -d, IFN α -5, IFN α -6, IFN α -4, IFN α -4b, IFN α -I,
IFN α -J, IFN α -H, IFN α -F and IFN α -8; is set forth in SEQ ID Nos. 1, 182, 185, 232, 183
and 186-195, respectively; and

residue 1 in each SEQ ID corresponds to residue 1 of the mature interferon-alpha
~~that is an IFN α -2b or an IFN α -2a or an IFN α -2C selected from among proteins comprising~~
~~one or more single amino acid replacements corresponding to the replacement in SEQ ID~~
~~NOS: 1, or 182, or 185 of: L by V at position 3; L by I at position 3; P by S at position 4; P~~
~~by A at position 4; R by H at position 12; R by Q at position 12; R by H at position 13; R by~~
~~Q at position 13; M by V at position 16; M by I at position 16; R by H at position 22; R by Q~~
~~at position 22; R or K by H at position 23; R or K by Q at position 23; F by I at position 27; F~~
~~by V at position 27; L by V at position 30; L by I at position 30; K by Q at position 31; K by~~

~~T at position 31; R by H at position 33; R by Q at position 33; E by Q at position 41; E by H at position 41; K by Q at position 49; K by T at position 49; E by Q at position 58; E by H at position 58; K by Q at position 70; K by T at position 70; E by Q at position 78; E by H at position 78; K by Q at position 83; K by T at position 83; Y by H at position 89; Y by I at position 89; E by Q at position 96; E by H at position 96; E by Q at position 107; E by H at position 107; P by S at position 109; P by A at position 109; L by V at position 110; L by I at position 110; M by V at position 111; M by I at position 111; E by Q at position 113; E by H at position 113; L by V at position 117; L by I at position 117; R by H at position 120; R by Q at position 120; K by Q at position 121; K by T at position 121; R by H at position 125; R by Q at position 125; L by V at position 128; L by I at position 128; K by Q at position 131; K by T at position 131; E by Q at position 132; E by H at position 132; K by Q at position 133; K by T at position 133; K by Q at position 134; K by T at position 134; Y by H at position 135; Y by I at position 135; P by S at position 137; P by A at position 137; M by V at position 148; M by I at position 148; R by H at position 149; R by Q at position 149; E by Q at position 159; E by H at position 159; L by V at position 161; L by I at position 161; R by H at position 162; R by Q at position 162; K by Q at position 164; K by T at position 164; E by Q at position 165; E by H at position 165;~~

~~— wherein residue 1 corresponds to residue 1 of the mature IFN α -2b or IFN α -2a cytokine set forth in SEQ ID NOS:1, 182 or 185.~~

7. (Currently amended) The interferon alpha cytokine of claim 1, wherein:

the cytokine is the unmodified interferon alpha cytokine is selected from among an interferon α 2b (IFN α -2b), an interferon α -2a (IFN α -2a), an interferon α -2c (IFN α -2c) and a consensus interferon alpha

~~— has more resistance to proteolysis than the unmodified cytokine; and~~

~~— the cytokine has one or more single amino acid replacements corresponding to replacements in SEQ ID NOS:1, or 182, or 185 of: F by V at position 27; R by H at position 33; E by Q at position 41; E by H at position 41; E by Q at position 58; E by H at position 58; E by Q at position 78; E by H at position 78; Y by H at position 89; E by Q at position 107; E by H at position 107; P by A at position 109; L by V at position 110; M by V at position 111; E by Q at position 113; E by H at position 113; L by V at position 117; L by I at position 117; K by Q at position 121; K by T at position 121; R by H at position 125; R by Q at position 125; K by Q at position 133; K by T at position 133; E by Q at position 159 and E by H at position 159.~~

8. (Currently Amended) An interferon alpha cytokine of claim 6, further comprising duo-amino acid replacements ~~corresponding to replacements in SEQ ID NOS:1 or 182~~ selected from among:

D by N at position 2 and P by S at position 4;
D by N at position 2 and P by T at position 4;
L by N at position 3 and Q by S at position 5;
L by N at position 3 and Q by T at position 5;
P by N at position 4 and T by S at position 6;
P by N at position 4 and T by T at position 6;
Q by N at position 5 and H by S at position 7;
Q by N at position 5 and H by T at position 7;
T by N at position 6 and S by S at position 8;
T by N at position 6 and S by T at position 8;
H by N at position 7 and L by S at position 9;
H by N at position 7 and L by T at position 9;
S by N at position 8 and G by S at position 10;
S by N at position 8 and G by T at position 10;
L by N at position 9 and S by S at position 11;
L by N at position 9 and S by T at position 11;
M by N at position 21 and K by S at position 23;
M by N at position 21 and K by T at position 23;
R by N at position 22 and I by S at position 24;
R by N at position 22 and I by T at position 24;
R or K by N at position 23 and S by S at position 25;
R or K by N at position 23 and S by T at position 25;
I by N at position 24 and L by S at position 26;
I by N at position 24 and L by T at position 26;
S by N at position 25 and F by S at position 27;
S by N at position 25 and F by T at position 27;
L by N at position 26 and S by S at position 28;
L by N at position 26 and S by T at position 28;
S by N at position 28 and L by S at position 30;
S by N at position 28 and L by T at position 30;

L by N at position 30 and D by S at position 32;
L by N at position 30 and D by T at position 32;
K by N at position 31 and R by S at position 33;
K by N at position 31 and R by T at position 33;
D by N at position 32 and H by S at position 34;
D by N at position 32 and H by T at position 34;
R by N at position 33 and D by S at position 35;
R by N at position 33 and D by T at position 35;
H by N at position 34 and F by S at position 36;
H by N at position 34 and F by T at position 36;
D by N at position 35 and G by S at position 37;
D by N at position 35 and G by T at position 37;
F by N at position 36 and F by S at position 38;
F by N at position 36 and F by T at position 38;
G by N at position 37 and P by S at position 39;
G by N at position 37 and P by T at position 39;
F by N at position 38 and Q by S at position 40;
F by N at position 38 and Q by T at position 40;
P by N at position 39 and E by S at position 41;
P by N at position 39 and E by T at position 41;
Q by N at position 40 and E by S at position 42;
Q by N at position 40 and E by T at position 42;
E by N at position 41 and F by S at position 43;
E by N at position 41 and F by T at position 43;
E by N at position 42 and G by S at position 44;
E by N at position 42 and G by T at position 44;
F by N at position 43 and N by S at position 45;
F by N at position 43 and N by T at position 45;
G by N at position 44 and Q by S at position 46;
G by N at position 44 and Q by T at position 46;
N by N at position 45 and F by S at position 47;
N by N at position 45 and F by T at position 47;
Q by N at position 46 and Q by S at position 48;

Q by N at position 46 and Q by T at position 48;
F by N at position 47 and K by S at position 49;
F by N at position 47 and K by T at position 49;
Q by N at position 48 and A by S at position 50;
Q by N at position 48 and A by T at position 50;
K by N at position 49 and E by S at position 51;
K by N at position 49 and E by T at position 51;
A by N at position 50 and T by S at position 52;
A by N at position 50 and T by T at position 52;
S by N at position 68 and K by S at position 70;
S by N at position 68 and K by T at position 70;
K by N at position 70 and S by S at position 72;
K by N at position 70 and S by T at position 72;
A by N at position 75 and D by S at position 77;
A by N at position 75 and D by T at position 77;
D by N at position 77 and T by S at position 79;
D by N at position 77 and T by T at position 79;
I by N at position 100 and G by S at position 102;
I by N at position 100 and G by T at position 102;
Q by N at position 101 and V by S at position 103;
Q by N at position 101 and V by T at position 103;
G by N at position 102 and G by S at position 104;
G by N at position 102 and G by T at position 104;
V by N at position 103 and V by S at position 105;
V by N at position 103 and V by T at position 105;
G by N at position 104 and T by S at position 106;
G by N at position 104 and T by T at position 106;
V by N at position 105 and E by S at position 107;
V by N at position 105 and E by T at position 107;
T by N at position 106 and T by S at position 108;
T by N at position 106 and T by T at position 108;
E by N at position 107 and P by S at position 109;
E by N at position 107 and P by T at position 109;

T by N at position 108 and I by S at position 110;
T by N at position 108 and I by T at position 110;
K by N at position 134 and S by S at position 136;
K by N at position 134 and S by T at position 136;
S by N at position 154 and N by S at position 156;
S by N at position 154 and N by T at position 156;
T by N at position 155 and L by S at position 157;
T by N at position 155 and L by T at position 157;
N by N at position 156 and Q by S at position 158;
N by N at position 156 and Q by T at position 158;
L by N at position 157 and E by S at position 159;
L by N at position 157 and E by T at position 159;
Q by N at position 158 and S by S at position 160;
Q by N at position 158 and S by T at position 160;
E by N at position 159 and L by S at position 161;
E by N at position 159 and L by T at position 161;
S by N at position 160 and R by S at position 162;
S by N at position 160 and R by T at position 162;
L by N at position 161 and S by S at position 163;
L by N at position 161 and S by T at position 163;
R by N at position 162 and K by S at position 164;
R by N at position 162 and K by T at position 164;
S by N at position 163 and E by S at position 165; and
S by N at position 163 and E by T at position 165;

~~wherein residue 1 corresponds to residue 1 of the mature IFN α -2b or IFN α -2a
cytokine set forth in SEQ ID NOS:1 or 182.~~

9.-20. (Cancelled)

21. (Currently Amended) An interferon alpha cytokine of claim 1, comprising two, three, four or five ~~more~~ amino acid replacements in its sequence of amino acids.

22. (Previously presented) The interferon alpha cytokine of claim 21 that is a modified IFN α -2b cytokine.

23. ((Currently Amended)) An isolated modified interferon alpha cytokine, ~~of claim 1, wherein the cytokine comprises~~ comprising the sequence of amino acids set forth in

any of SEQ ID NOS: 2-17, 19-131, 134-181, 978-988 ~~or~~ and 1303, wherein the arginine at position 23 in each SEQ ID is replaced with a lysine.

24-39. (Canceled)

40. (Original) A pharmaceutical composition, comprising a cytokine of claim 1 in a pharmaceutically acceptable carrier.

41-45. (Cancelled)

46. (Withdrawn, Amended) An The interferon alpha cytokine of claim ~~44~~ 1, selected from among an IFN α -2a, an IFN α -c, an IFN α -2c, an IFN α -d, an IFN α -5, an IFN α -6, an IFN α -4, an IFN α -4b, an IFN α -I, an IFN α -J, an IFN α -H, an IFN α -F, an IFN α -8, and an IFN α -consensus cytokine.

47.- 278 (Cancelled)

279. (Currently Amended) An interferon alpha cytokine of claim 1 ~~selected from among modified cytokines,~~ comprising a the sequence of amino acids set forth in ~~any of SEQ ID NOS: 2-181, 978-988 or 1303~~ NO: 87 or an interferon alpha structural homolog thereof.

280-306. (Cancelled)

307. (Currently amended) An interferon alpha cytokine of claim 1 that is an IFN α -2b, ~~an IFN α -2a, or an IFN α -2c~~ cytokine selected from proteins comprising one or more single amino acid replacements corresponding to the replacement in ~~any of SEQ ID NOS: 1, 182, 185 or 232~~ of: L by V at position 3; L by I at position 3; P by S at position 4;; P by A at position 4; R by H at position 12; R by Q at position 12; R by H at position 13; R by Q at position 13; M by V at position 16; M by I at position 16; R by H at position 22; R by Q at position 22; R or K by H at position 23; R or K by Q at position 23; F by I at position 27; F by V at position 27; L by V at position 30; L by I at position 30; K by Q at position 31; K by T at position 31; R by H at position 33; R by Q at position 33; E by Q at position 41; E by H at position 41; K by Q at position 49; K by T at position 49; E by Q at position 58; E by H at position 58; K by Q at position 70; K by T at position 70; E by Q at position 78; E by H at position 78; K by Q at position 83; K by T at position 83; Y by H at position 89; Y by I at position 89; E by Q at position 96; E by H at position 96; E by Q at position 107; E by H at position 107; P by S at position 109; P by A at position 109; L by V at position 110; L by I at position 110; M by V at position 111; M by I at position 111; E by Q at position 113; E by H at position 113; L by V at position 117; L by I at position 117; R by H at position 120; R by Q at position 120; K by Q at position 121; K by T at position 121; R by H at position 125; R by Q at position 125; L by V at position 128; L by I at position 128; K by Q at position 131;

~~K by T at position 131; E by Q at position 132; E by H at position 132; K by Q at position 133; K by T at position 133; K by Q at position 134; K by T at position 134; Y by H at position 135; Y by I at position 135; P by S at position 137; P by A at position 137; M by V at position 148; M by I at position 148; R by H at position 149; R by Q at position 149; E by Q at position 159; E by H at position 159; L by V at position 161; L by I at position 161; R by H at position 162; R by Q at position 162; K by Q at position 164; K by T at position 164; E by Q at position 165; and E by H at position 165 or any combination thereof, wherein residue 1 corresponds to residue 1 of the mature IFN α -2b or IFN α -2a cytokine set forth in SEQ ID NOS:1 or 182.~~

308. -340. (Cancelled)

341. (Currently Amended) The interferon alpha cytokine of claim 1, comprising that contains only a single amino acid replacement corresponding to the replacement in SEQ ID NOS: 1, or 182 or 185 of E by Q at position 41 compared to the interferon cytokine that does not include the E41Q replacement.

343. (Previously Presented) The pharmaceutical composition of claim 40, formulated for oral administration.

344. (Cancelled)

345. (Previously presented) The An interferon alpha cytokine of claim 1, comprising the sequence of amino acids set forth in SEQ ID NO:87.

346. (Cancelled)

347. (Currently Amended) The interferon alpha cytokine of claim 1, comprising two amino acid replacements that has one or two replacements compared to the unmodified interferon alpha cytokine.

348. (New) A modified interferon (IFN) alpha cytokine, comprising one or two amino acid replacements, wherein one replacement is E41Q.

349. (New) The modified IFN alpha cytokine of claim 348 that is an IFN- α 2b cytokine.

350. (New) A pharmaceutical composition, comprising a cytokine of claim 348 in a pharmaceutically acceptable carrier.

351. (New) A pharmaceutical composition, comprising a cytokine of claim 349 in a pharmaceutically acceptable carrier.

352. (New) A pharmaceutical composition, comprising a cytokine of claim 307 in a pharmaceutically acceptable carrier.

353. (New) The pharmaceutical composition of claim 352 that is formulated as a tablet or capsule for oral administration.

354. (New) A pharmaceutical composition, comprising a cytokine of claim 345 in a pharmaceutically acceptable carrier.

355. (New) The modified interferon alpha cytokine of claim 22, comprising amino acid replacements corresponding to E41Q and D94G.

356. (New) The modified interferon alpha cytokine of claim 6, wherein the unmodified interferon alpha cytokine is selected from among an interferon α 2b (IFN α -2b), an interferon α -2a (IFN α -2a), an interferon α -2c (IFN α -2c) and consensus interferon.